UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,910	05/11/2001	Annette Gilchrist	2661-101	4758

6449 7590 07/08/2005

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,910	GILCHRIST ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-9 and 12-101* is/are pending in the application.

4a) Of the above claim(s) *2,12,20,25-32 and 34-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-9,13-19,21-24 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/28/05 has been entered.

Status of Claims

Claims 1-3, 5-9, 12-101 are pending in the application.

Claims 2, 12, 20, 25-32 and 34-101 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and specie, as stated above.

Claims 1, 3, 5-9, 13-19, 21-24 and 33 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-9, 13-19, 21-24 and 33 as amended, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method utilizing a biased library based from a native G protein Gα-subunit carboxyl terminal and specific peptide library for the candidate compounds does not reasonably provide enablement for a method using any or all types of a native Gα-subunit carboxyl terminal for the peptide library or candidate compounds for reasons advanced in the last Office action.

Response to Arguments

Applicants state that the Office Action cites reasons as advanced in an Office Action dated April 17, 2003. Since there is no Office Action of that date in the present application, Applicants assume the Action dated June 11, 2003 was meant to be cited and will reply based on the reasons given on pages 5-9 of this Office Action.

In reply, as correctly pointed out by applicants, there is no April 17, 2003 Office action. Rather, the Office action was mailed on June 11, 2003. The error is regretted.

As an initial matter, Applicants point out that there is no "Gα-coupled receptor" recited in the specification or claims of this application, or known to Applicants. The G protein

comprises a Gα-subunit, however there is no specific Gα-coupled receptor (GPCR) that is coupled to Gα-distinct from G proteins, nor is Gα- a type of GPCR. Gα-is not a type of G protein or a type of G protein coupled receptor. Rather a subunit common to all G proteins. The Office Action also seems to assume that G proteins are GPCR ligands. This also is not true; ligands and G proteins bind to GPCRS at different sites, now referred to as orthosteric and allosteric sites, respectively. Because at least some of the bases for rejection of the pending claims appear to relate to this type of misunderstanding concerning the molecules of the invention, Applicants have amended the claims for the sake of clarity and to assist the reader in understanding the molecules involved and their relationship to one another. Therefore, the term G protein coupled receptor has been replaced with the acronym GPCR in the claims to reduce repetition of the phrase "G protein" and reduce the potential for confusion between G protein coupled receptor and G protein.

In response, the examiner gratefully appreciates applicants' differentiation, clarification and amendments of the claims. The amendment removed the confusion and misunderstanding of the different terms used in the claims.

Applicants argue that the claims do not involve a library derived from any receptor; not from any GPCR nor from any "Gα-coupled receptor. The claims recite providing a peptide library which is based on a native G protein peptide, not a G protein coupled receptor (GPCR) peptide. Therefore, the Office's stated reasoning is specious because: (1) there is no Gα--coupled receptor; (2) the peptide libraries recited in the claims are not derived from GPCR or any species of GPCR.

In reply, the lack of enabling disclosures is still maintained albeit; a misunderstanding of the different claimed terminologies was used. The lack of adequate enabling disclosure is based on the broad scope of the components as used in the broad method steps. The Examples, as stated by applicants at page 21 of the instant REMARKS are based on the ***single*** carboxyl terminal sequence of Gαt (Seq. ID. No. 139). Gαt is but only one of the species of Gα subunit, which in turn is a subunit of G proteins. Gαt, alone, already includes a huge species from one type of G alpha subunit of a G-protein. How much more for the numerous different types of species (e.g., Gαt) included in G-alpha subunit carboxyl G-protein? A listing of every possible Gαt, a species of Gα, from a single native G-protein does not constitute an enabling disclosure for every

species in a genus. It would not "reasonably lead" those skilled in the art to any particular species (of the genus of a G alpha subunit carboxyl of a G-protein). In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967). This does not take into consideration the numerous variations encompassed by the variant peptides based on said carboxyl subunit of G-protein.

Applicants state that the Office criticizes the assay described in the specification because it is able to discriminate among analogs that have different levels of binding from no effect to significant effect and because the binding of G protein to GPCR is specific. The Office seems to equate the discrimination of the assay with unpredictability. This logical connection does not hold. The screen provided by the Applicants here enables the user to determine whether a given compound specifically binds to a GPCR, thus eliminating any perceived "unpredictability" in determining what compounds bind. The Office is arguing that the assay's results are unpredictable because it cannot be known in advance of performing the assay whether a difference in one amino acid affects binding of a G protein peptide to its receptor (i.e. some analogs tested had significant effects and some did not). It is the nature of screening assays, as is well known in the art, that some compounds are positive and many are not. If the results were

predictable in advance of performing the screen, there would be no need to perform the screen or any screen. In effect, the Office is arguing that because the screen provides an answer to an otherwise unpredictable question, the assay itself is unpredictable. If such were the case, no screening assay would be useful. For example, a screen for HIV in blood would be considered unpredictable and not enabled unless either all blood samples contained HIV or the user could pre-select only positive samples for testing. Applicants submit that such a test would be useful, workable and enabled even if blood samples provided positive results because the purpose of the assay is to determine whether the sample contains HIV or not.

In response, it is not the nature of the assay and/or its capability to do its function that is at issue. The issue is whether the assay that is used for the known, single and defined library would be applicable or predictive for an assay of a library having no defined structure, as claimed. As already shown for the single, defined compound library, a single residue variation did not produce the desired object of the invention. The assay method is but one of the numerous unpredictable factors included in the broad scope of the method. Other factors like the undefined structure of the library, the variations in the library and library of candidate compounds are all

determinative of the unpredictable effects of the claimed method. In assays involving HIV, unpredictability is not an issue. The virus, HIV, being assayed is known and a specific assay method adapted for its determination irrespective of the type of blood samples. The assay does not screen for any type of viruses.

Applicants state that the Office should not penalize Applicants because they have invented a method to screen more reliably for an event that is rare or that could not previously be predicted. In the drug discovery art, practitioners routinely screen millions of compounds and obtain positive results in the tens or hundreds, many of which are false positives or only weak responders.

In reply, applicants are not being penalized for inventing a method of screening reliably an event. Rather, that the event that applicants are screening is for a particular event and not commensurate with the huge scope of the claims. Screening millions of compounds is known in the art. However, what is also known in the art is that such screening can only be achieved for a compound of defined structure e.g., a library of known constituent as done in the specification.

Applicants cite paragraphs 52-55 of the specification, which describe the nature of the G protein/GpcR interactions

useful for screening methods and providing a number of examples. Table III, on page 24, provides several dozen specific examples of different G proteins suitable on which to base library construction. To state that the specification lacks guidance as to which G proteins on which one should base the library is simply unreasonable.

In response, it is not controverted that the specification specifically Table III present specific examples of different G proteins that forms the basis of a library construction. However, the claims do not recite only different G proteins but a variant library based on the different G proteins. Thus, applicants cannot import limitations in the specification into the claims. The claims do not recite any compounds from Table III.

Applicants state that the construction of peptide libraries per se, and peptide display libraries, is not new in the art. This type of construction was not considered unreliable or unpredictable in its function at the time this application was filed. Applicants cite several references, e.g., Gilchrist et al., Meth. Enzymol. 315:388-404, 2000. These references all bear dates before or near this application's filing date and describe methods for making and using peptide libraries. The concerns articulated in the Office Action were known in the art. Various

methods were in use to overcome them. Therefore, the art enables the use of peptide libraries. What is known in the art is not necessary to include in the specification for enablement of the claimed invention and preferably is omitted from the specification of a patent application. M.P.E.P. 52164.01.

In response, construction of peptide libraries per se is known in the art but only if the compounds present in the library is known such that a library (not variants) can be made. The references provided by applicants evidenced such. There is nothing in any of these references that make a library having no definite structure or the compounds contained in the library including variations thereof. What is known in the art can be omitted in patent application. But applicants fail to point out where in the art a library of no definite constitution has been made. If applicants choose to rely on the prior art to render his disclosure enabling, the applicants must show that anyone skilled in the art would have actually possessed the knowledge, In re Lange (CCPA 1981) 644 F2d 856, 209 USPQ 288, or would reasonably be expected to check the source which applicants rely upon to complete his disclosure and would be able to locate the information with no more than reasonable intelligence. In re Herschler (CCPA 1979) 200 USPQ 711; In re Albrecht II (CCPA 1975) 185 USPQ 590. Not every thing which may be cited as prior art to

preclude the grant of a patent can be equated with common knowledge for the purposes of meeting the enablement requirement of 112.

Applicants argue that Examples 1 and 2 alone provide a working example showing successful construction of 6 different libraries with greater than 109 independent clones per microgram of vector each. Examples 7-9 demonstrate that the libraries can be used in "panning" to identify strong binders. Applicants submit that this working example, along with the discussion in the specification and what is known in the art, provides more than sufficient guidance to the skilled reader as to how to make these types of libraries.

In response, the Examples enable the specifics of the claimed method is not controverted. However, the issue is the enabling disclosure for the huge scope of the claimed genus. None of the claimed generic component defines any structure e.g., the variant peptide library, except that it is based on G alpha subunit of the carboxyl G-protein. A variant peptide library encompasses the different types of substitutions, additions, deletions, singly or in combinations even for one species listed in Table III of the specification. The claims do not recite a single kind of variant library.

Applicants state that the types of peptide expression systems are not new to the art, and as discussed above are not necessary to be described in minute detail to enable the claims pending here. The methods described here for presentation of peptides were successful with high transformation efficiencies. See specification at paragraphs 58-59. The performance of individual cells in the expression system is not relevant since individual cells are not assayed separately. The library is provided in the form of a bacterial lysate or a purified fusion protein, for example, and not as a single cell or clone of cells. Moreover, these methods are well-accepted to function as they are described in the present application to present and display any peptide, for example the many peptides screened in the examples provided here and in the art. See, for example, references cited above.

In response, the cited references describe expression system specifically adapted for the specific compounds at hand. The expression systems are not new in the art. But it is also known in the art that in order for the expression systems to express the compounds, the compounds transforming the system is known or of defined structure.

Applicants state that the Office Action states that the art is inherently unpredictable because insertion of a foreign

sequence into a protein may have unpredictable effects on the protein or its expression, thus likely perturbing the function and stability of the fusion. This criticism is again merely a repeated statement that the Office doubts the workability of the display libraries taught for use in some embodiments of the present invention. Applicants and others have routinely used these library expression methods. See citations above relevant to this subject matter. Completely functional libraries are reported in the specification, along with the screen results of several working examples. Applicants refer again to Examples 1 and 2, which show successful construction of 6 different libraries with greater than 109 independent clones per microgram of vector each. The methods work, and they have been demonstrated to have worked with several different libraries containing 109 independent clones based on several different peptide sequences.

In response, a review of the cited references, e.g., Zwick shows that there are no generalities that can be made in this highly unpredictable peptide art. Zwick at page 432, Conclusions section state " as new libraries are constructed their value would be more clearly demonstrated were they tested side-by-side along with several other different libraries in screenings against a variety of receptors……as it stands now, most

researches only test a single library at a time using screening methods that are usually not optimized. The results of side-by-side comparisons between different library would clarify the types of libraries that most effectively produce ligands for a given type of receptor or Ab, whether there are any general rules that govern the types of libraries that contain ligands for a particular class of receptor.. …"

Applicants argue that the Office has provided no reasoning why the skilled person would not be able to repeat the types of assays reported in the specification using any suitable, known library or would believe that the methods do not work as disclosed. There would be any doubt in the mind of the skilled reader that these methods would have been considered routine given the art and the discussion and examples provided by Applicants.

In reply, attention is directed to the numerous prior art cited by applicants, inter alia, Zwick. Thus, as a skilled artisan in the field knows, a method e.g., phage display library can only be routine given the structure or formula of a compound. However, for a compound, as the instant variant library of no defined structure, it is not seen how this can be a routine endeavor. Except for the generalities made in the

specification, the enabling disclosure is not commensurate with the huge scope of the generic claim.

Much of applicants' subsequent arguments are either that the method is known or routine in the art or provided in the Examples and in the specification. The reasons set forth above, address applicants' statement as to the arguments as to what is considered known or routine in the art or that the Examples enable the claimed method.

[Incorporating the sequences listed at Table III of the specification to form a variant peptide library would obviate this rejection.]

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5-9, 13-19, 21-24 and 33, as amended, are rejected under 35 U.S.C. 103(a) as being obvious over Fowlkes et al (WO 98/19162) in view of Gilchrist (The Journal of Biological Chemistry) for reasons set forth in the Office action.

Response to Arguments

Applicants recognize that Fowlkes et al. discusses only receptor ligands but argue that Fowlkes does not relate in any way to screen that assay for binding to G protein interaction sites on a GPCR. Fowlkes does not even mention G protein/GpcR interactions on the intracellular face of the receptor. Applicants urge that Fowlkes does not discuss an assay for identifying molecules that interfere with G protein signaling. They do not teach or suggest a two-step screening assay. They do not teach, suggest or even hint at a library of variant peptides based on the primary sequence of a native G protein Ga subunit carboxyl terminal peptide sequence that binds to a GPCR on an intracellular location of the GPCR and therefore cannot teach, suggest or even hint at methods that perform steps (b) and (c). There is no disclosure or suggestion of a second screening step at all, much less the step of (e), which recites screening in competition with a library member selected in step (c). The method of Fowlkes et al does not result in identification of a GPCR signaling inhibitor. Applicants state that the Office has cited Gilchrist et al to make up for these enormous deficiencies. This reference is cited for teaching on pages 14913-14918, a carboxyl-terminal G-alpha subunit-based combinatorial peptide library that is screened for binding to

adenosine receptors and then in agonist-antagonist competition. This description of the teachings and fair description of the Gilchrist reference is not accurate and is misleading. Gilchrist et al. disclose peptide analogs of G-alpha peptides and testing of their ability to bind a GPCR and stabilize it in a particular conformation. The assays of Gilchrist et al. involve competition of an agonist and antagonist of the GPCR at the ligand-binding site, not competition at the G protein/GpcR interaction site. (The claims here do not relate to the orthosteric ligand binding site but rather an allosteric site on the GPCR). As traditional orthosteric ligands, they bind at the extracellular ligand binding site and do not bind at the G protein interaction site of the GPCR.

In reply, one cannot show non-obviousness by attacking the references individually where the rejection is based on a combination of references. In re Young, 159 USPQ 725 (CCPA 1968). The test for obviousness under 35 USC 103 is not the express suggestion of the claimed invention in any or all of the references but what the references taken collectively would suggest; and inferences which one skilled it in the art would reasonably be expected to drawn from the disclosure in the references. In re Preda, 159 USPQ 342 and In re Conrad, 169 USPQ 170.

Fowlkes et al teach at page 10, line 19 up to page 13, line 15; the abstract and claims, the claimed two-screen method. In the abstract, Fowlkes teaches a method for identifying a ligand which mediates the biological activity of a target protein by inhibiting an inhibition of the binding of to a binding partner, comprising: (a) screening a first combinatorial library comprising first member ligands for binding to the target-binding ligands (TBLs), to identifying one or more TBLs; (b) screening a second library comprising second member ligands for the ability to inhibit the binding of one or more of the TBLs to the target protein, thereby obtaining one or more inhibitory ligands; and (c) determining which of the inhibitory ligands can mediate a biological activity of the target protein. See further the claims. While Fowlkes uses the traditional ligand-receptor binding however, Gilchrist teaches the motivation of non-traditional G-protein binding GPCR. Gilchrist teaches at page 14912 that "traditionally, the agonist binding site is the point of intervention, but in some cases receptor subtype-selective drug have been difficult to achieve. Another possible target for inhibition is the receptor-G protein interface, which as been defined in some detail and involves the intracellular loops of the seven-transmembrane helix receptors with several regions on heterotrimeric G proteins…" As stated by applicants above,

GPCRS are activated via ligands acting at the orthosteric binding site (on the extracellular face of the plasma membrane). ***Ligand binding induces conformational changes that subsequently lead to G protein association with the GPCR.*** It would be within the ordinary to determine whether the ligand binding receptor of Fowlkes induces conformation changes that eventually leads to G protein association with GPCR i.e., in the intracellular level.

In the absence of new and unexpected results of using a different pathway of interaction i.e., G protein/GPCR instead of the ligand/GPCR binding of Fowlkes, the claimed method is prima facie obvious to one having ordinary skill in the art at the time of filing.

The 103 rejection over Coughlin is withdrawn in view of the amendments to the claims and applicants' arguments.
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the

organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
July 5, 2005